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Mild and Efficient α-Chlorination of Carbonyl Compounds Using Ammonium Chloride and Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)

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A simple protocol for the α-monochlorination of ketones and 1,3-dicarbonyl compounds utilizing NH_4Cl as a source of chlorine and Oxone as an oxidant in methanol without catalyst is presented. The reaction proceeds at ambient temperature in yields ranging from moderate to excellent.

α-Haloketones are important synthetic intermediates and are used as precursors for various organic transformations. Among them, α-chloroketones have received considerable attention because of their versatile applications in organic synthesis and their high reactivity makes them react with a large number of nucleophiles to provide a variety of useful compounds.[1] They also serve as metabolically more stable alternatives to hydrogen and methyl functionality in drugs without loss of therapeutic efficacy.[2]

Synthesis of α-chloroketones has usually been achieved by indirect routes, which include the reaction of silyl enol ethers with transition-metal chlorides[3] and reaction of aromatic compounds with chloroacetyl chloride.[4] Direct conversion of ketones into α-chloroketones is an important synthetic transformation that has received considerable attention. Generally the direct chlorination can be accompanied by using chlorination agents such as copper(II) chloride,[5] *p*-toluenesulfonyl chloride,[6] sulfuryl chloride,[7] tetraethylammonium trichloride,[8] and *N*-chlorosuccinimide.[9]

Recently several procedures and reagent combinations have been reported for the α-chlorination of ketones. These include: $(CH_3)_3SiCl–KNO_3$,[10] DCDMH (1,3-dichloro-5,5-dimethylhydantoin),[11] *N*-halosuccinimide (NCS)–solvent free conditions,[12] *N*-halosuccinamide–DMSO,[13] NCS–UHP (urea–hydrogen peroxide) in ionic liquid,[14] $[Hmim][NO_3]–HCl$,[15] $AlCl_3$/Urea–H_2O_2 in ionic liquid,[16] NCS–Amberlyst-15,[17] HTIB ([hydroxy(tosyloxy)iodo]benzene)–$MgCl_2$–MW,[18] NCS–Lewis acid,[19] NCS–thiourea,[20] $NaClO_2–[Mn(acac)_3]$–alumina,[21] $(CH_3)_3SiCl$–DMSO,[22] and $(CH_3)_3SiCl–SeO_2$.[23] However, most of these methods have drawbacks such as use of costly, hazardous or toxic reagents with potential environmental problems due to the generation of hazardous waste and require tedious work up procedures. Therefore, there is still a need to develop more convenient, efficient, eco-friendly, and selective procedures for the α-monochlorination of carbonyl compounds. From the green-chemistry point of view, a noncatalytic process is very significant and alternative for synthetic organic chemistry.

In our on-going efforts to achieve environmentally friendly halogenation procedures,[24] earlier we have reported the aromatic chlorination using NH_4Cl–Oxone without catalyst[25] and to the best of our knowledge, there are no reports of selective α-chlorination of ketones or 1,3-dicarbonyl compounds using NH_4Cl and Oxone. Here we wish to report that the NH_4Cl–Oxone reagent system can be used for the direct α-monochlorination of ketones and 1,3-dicarbonyl compounds.

Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$), a potassium triple salt containing potassium peroxymonosulfate, is an effective oxidant. Owing to its stability, water solubility, ease of transport, nontoxic (green) nature, and cost-effectiveness, this oxidant has become an increasingly popular reagent for several oxidative transformations.[26]

First, acetophenone was chosen as a model substrate for chlorination in order to find optimal conditions. Several solvents were investigated and results revealed that reaction was dependent on polarity of solvent and miscibility of reagents in reaction media (Table 1). The best results were obtained when MeOH was used as a solvent among others in terms of reaction yields and time, probably due to its high polarity and solubility of NH_4Cl and acetophenone in reaction media. On the other hand EtOH, CH_3CN, or THF used as solvents afforded lower yields even after 24 h, possibly due to poor solubility of NH_4Cl in these solvents. This transformation was also attempted in other solvents such as acetone, ethyl acetate, DCM, $CHCl_3$, or CCl_4. The reaction barely took place and nearly no conversion of acetophenone was observed, maybe due to the low polarity of solvents and insolubility of NH_4Cl in these solvents. Despite complete solubility of NH_4Cl and Oxone in water (highly polar solvent), the yield was very low due to poor solubility of acetophenone in water. 1.1 equivalent of NH_4Cl–Oxone afforded better results than to 1.0 equivalent of NH_4Cl–Oxone.

Having optimized the reaction conditions, we continued our investigation with various structurally different carbonyl compounds. A variety of aryl alkyl ketones, aliphatic ketones and 1,3-dicarbonyl compounds were reacted smoothly under the present reaction conditions to provide the corresponding α-chlorinated products in moderate to excellent yields.[27] The

Table 1. α-Chlorination of acetophenone: effect of solvent[a]

Entry	Solvent	Time/h	Yield/%[b]
1	CH_3OH	9	97
2	CH_3OH[c]	12	93
3	EtOH	24	13
4	CH_3CN	24	30
5	THF	24	25
6	Acetone	24	—
7	Ethyl Acetate	24	—
8	DCM	24	—
9	$CHCl_3$	24	—
10	CCl_4	24	—
11	H_2O	24	9

[a]Acetophenone (2 mmol), NH_4Cl (2.2 mmol), Oxone (2.2 mmol), solvent (10 mL), room temperature. [b]The products were characterized by NMR, mass spectra and quantified by GC. [c]Acetophenone (2 mmol), NH_4Cl (2 mmol), Oxone (2 mmol), solvent (10 mL), room temperature.

results are summarized in Tables 2 and 3. The structural identity of all the products was ascertained on the basis of their spectral properties (^{1}H, ^{13}C NMR and mass spectra, see Supporting Information).[28]

As can be seen from Table 2, acetophenone was converted to the respective α-chlorinated product in high yield (97%) within 9 h at room temperature. In order to determine the influence of the substituent on an aromatic ring on the reaction path with this reagent system, we have carried out the chlorination reaction with acetophenone containing electron-donating or -withdrawing functional groups at different positions.

Acetophenone containing electron-donating groups were of higher reactivity than ones containing electron-withdrawing groups under similar reaction conditions. Activated acetophenones gave exclusively corresponding α-chlorinated products in high yields at room temperature (Table 2, Entries 2–6). Whereas, deactivated acetophenones furnished the α-chlorinated products, along with substantial amount of α-chlorodimethyl ketals at room temperature and exclusively α-chlorinated products at reflux temperature (Table 2, Entries 7–14). In the case of methoxy- or hydroxyacetophenone, methoxy or hydroxy groups did not direct chlorination to the ring position and effectively chlorinated at the side chain (Table 2, Entries 5 and 6).

1-Tetralone (non-methyl ketone) also reacted smoothly and yielded the respective α-chlorinated product in near quantitative yield (96%) in 7 h under similar conditions (Table 2, Entry 16). In the case of 5-methoxy-1-tetralone, activation of the aromatic ring with methoxy substituent did not interfere with the regioselectivity of the chlorination and α-chlorination was achieved in moderate yield (53%) even after 24 h (Table 2, Entry 17).

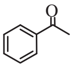
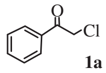
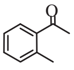
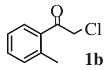
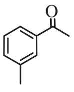
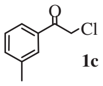
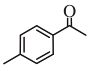
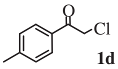
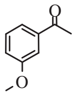
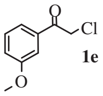
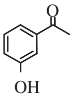
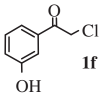
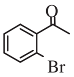
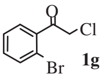
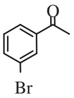
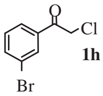
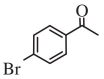
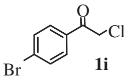
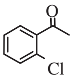
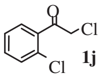
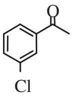
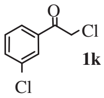
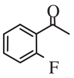
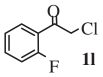
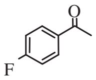
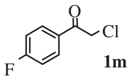
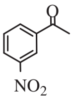
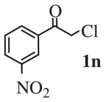
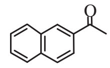
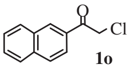
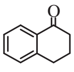
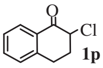
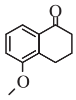
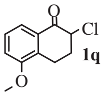
We next explored the scope of the present method by treating aliphatic ketones under the present reaction conditions. As can be seen from Table 3, 4-methyl-2-pentanone was selectively chlorinated at the 1-position to afford 1-chloro-4-methyl-2-pentanone in 89% yield (Table 3, Entry 1), whereas, 2-nonanone and 3-octanone produced a regioisomeric mixture of monochlorinated products (Table 3, Entries 2 and 3).

Further, we investigated the efficiency of the method with 1,3-dicarbonyl compounds. In recent years, chlorination at the 2-position of 1,3-dicarbonyl compounds received much attention because of versatile utilities of 2-chloro-1,3-dicarbonyl compounds in organic synthesis.[29] As highlighted in Table 3, 2-unsubstituted and 2-substituted 1,3-keto esters were converted to their corresponding 2-chloro products in high yields using this procedure. In some cases dichlorination was also observed.

In a blank experiment, reaction was performed with acetophenone and NH_4Cl in the absence of Oxone under similar reaction conditions and the reaction did not succeed. Thus, the role played by the Oxone (oxidant) was justified. We propose a plausible reaction mechanism for the α-chlorination of ketones is shown in Scheme 1. It is assumed that Oxone oxidizes the Cl^- (NH_4Cl) to Cl^+ (HOCl),[30] which further reacts with enol form of ketone to afford the corresponding α-chlorinated product.

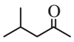
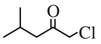
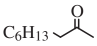
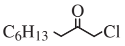
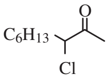
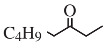
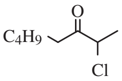
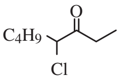
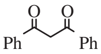
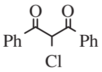
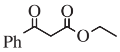
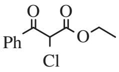
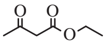
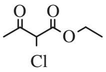
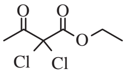
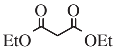
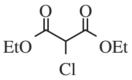
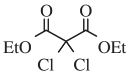
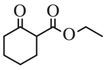
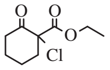
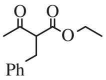
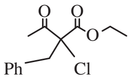
In summary, we have presented a novel and efficient approach for the α-chlorination of various ketones and 1,3-dicarbonyl compounds using NH_4Cl/Oxone in MeOH. The present protocol is more attractive than the earlier methods, offers additional advantages such as commercial availability of the reagents, high yields, formation of cleaner products, mild reaction conditions, no evolution of hydrogen chloride, and

Table 2. α-Chlorination of aryl ketones using NH_4Cl and Oxone[a]

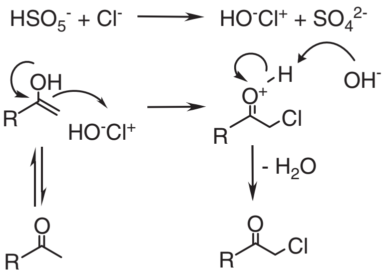
Entry	Substrate	Time/h	Product	Yield/%[b]
1		9	 **1a**	97
2		15	 **1b**	96
3		11	 **1c**	85
4		9	 **1d**	94
5		7	 **1e**	82
6		24	 **1f**	76
7		22 5[c]	 **1g**	20 (40)[d] 84
8		24 3[c]	 **1h**	43 (29)[d] 98
9		24 1.4[c]	 **1i**	65 (10)[d] 98
10		48 10[c]	 **1j**	33 (39)[d] 84
11		48 6[c]	 **1k**	43 (20)[d] 98
12		48 5[c]	 **1l**	46 (31)[d] 98
13		48	 **1m**	85
14		48	 **1n**	19 (29)[d]
15		24	 **1o**	90
16		7	 **1p**	96
17		24	 **1q**	53

[a] Substrate (2 mmol), NH_4Cl (2.2 mmol), Oxone (2.2 mmol), methanol (10 mL), room temperature. [b] The products were characterized by NMR, mass spectra and quantified by GC. [c] At reflux temperature. [d] α-Chlorodimethyl ketal.

Table 3. α-Chlorination of aliphatic ketones and 1,3-dicarbonyl compounds using NH_4Cl and Oxone[a]

Entry	Substrate	Time/h	Product (Yield/%)[b]
1		9.3	 (89) **2a**
2		3.3	 (46) **2b**
			 (37) **2c**
3		7.4	 (61) **2d**
			 (38) **2e**
4		5	 (95) **2f**
5		5	 (94) **2g**
6		6	 (66) **2h**
			 (12) **2i**
7		24	 (10) **2j**
			 (45) **2k**
8		4	 (80) **2l**
9		10	 (92) **2m**

[a]Substrate (2 mmol), NH_4Cl (2.2 mmol), Oxone (2.2 mmol), methanol (10 mL), room temperature. [b]The products were characterized by NMR, mass spectra and quantified by GC.



Scheme 1. Plausible reaction mechanism.

environmentally friendly nature. Hence it offers useful alternative to the existing methods.

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References and Notes

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27 **General procedure for the chlorination of carbonyl compounds**: Oxone (2.2 mmol) was slowly added to a well stirred solution of NH_4Cl (2.2 mmol) and carbonyl compound (2 mmol) in methanol. Then the reaction mixture was allowed to stir at room temperature, until carbonyl compound completely disappeared (monitored by TLC) or an appropriate time. Upon the completion of reaction, the mixture was filtered, solvent was removed under reduced pressure and ethyl acetate (20 mL) was added to the residue. The ethyl acetate solution was washed with water (2 × 30 mL) and organic layer was dried over Na_2SO_4. After evaporation of the solvent the residue was purified by column chromatography using silica gel (230–400 mesh) to give pure α-chlorinated products.

28 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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